IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/084,676	Confirmation No.	: 2539
First Named Inventor	: Iris ZIEGLER		
Filed	: February 28, 2002		
TC/A.U.	: 1618		
Examiner	: Blessing Fubara		
Docket No.	: 029310.50932		
Customer No.	: 23911		
Title	: Oral Pharmaceutical Forms of Administration with a Delayed Action		

REPLY BRIEF UNDER 37 C.F.R. §41.41

Mail Stop APPEAL BRIEF
Commissioner for Patents
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Sir:

This is a Reply Brief in response to the Examiner's Answer mailed March 20, 2008 in the appeal of the above-identified patent application.

The language of Claim 17 speaks for itself and expressly calls for a "Compound" of tramadol hydrochloride and diclofenac sodium.

Claim 17 is directed to a "compound" of tramadol hydrochloride and diclofenac sodium which is formed *in situ* and which has a water solubility of less than or equal to 100 mg/ml. The Examiner's comments at the top of page 5 of the Examiner's Answer indicate that the Examiner doubts whether a "compound" exists. Thus, the Examiner states that "Claim 17 is thus examined as a mixture of tramadol-HCl and diclofenac-sodium." But that is not what the claim says. The claim language calls for a compound. The issue of whether a new chemical entity is formed is irrelevant to the question of definiteness. Definiteness of the

claim depends solely on whether a person skilled in the art can determine what the claim calls for. In this case, a person skilled in the art can readily understand that the claim calls for a compound. Consequently, the claim is not indefinite.

The fact that the claim uses the word "comprising" and thus is open to the inclusion of additional unspecified ingredients also does not render the claim indefinite. Presumably, such unspecified ingredients could even include tramadol and diclofenac individually. However, the claim expressly calls for a compound of tramadol hydrochloride and diclofenac sodium formed *in situ* and having a solubility less than or equal to 100 mg/ml. The claim does not read on a mixture of tramadol and diclofenac which does not include such a compound. It expressly and explicitly requires the presence of a compound of the two. Thus, the claim says what it means, and means what it says.

The Evidence of Record Establishes that a "Compound" is formed.

The evidence of record establishes that the Examiner's doubts are unfounded. The Declaration of Dr. Ziegler presents a direct comparison of the properties of tablets containing a mixture of tramadol hydrochloride and diclofenac sodium and comparable tablets containing the claimed compound.

The graph at the top of page 5 of the Ziegler Declaration shows the strikingly different release rates of active ingredient from the tablets containing the compound of the invention compared to the tablets containing the mixture.

The tablets containing the mixture release 100% of the active ingredients in only about 20 minutes, whereas the tablets containing the compound of the invention do not achieve complete release of the active ingredients until approximately 8 hours or more. This shows that the claimed invention is not just a mixture of tramadol hydrochloride and diclofenac sodium.

Moreover, the striking difference in solubility between the simple mixture of tramadol hydrochloride and diclofenac sodium and the compound of the invention is clear evidence that one cannot simply assume, as the Examiner argues in her Answer (see paragraph j on page 12) that a mixture would inherently have a water solubility less than or equal to 100 mg/ml. The objective test evidence suggests otherwise.

Similarly, the differential scanning calorimetry (DSC) spectra attached to the Ziegler Declaration as Exhibits A through E evidence the existence of a new chemical entity, i.e. a new compound, in the present invention. This is clearly seen in the pronounced peak at approximately 292°C which is present in the spectrum of the sample containing the compound of the invention, but not in the spectra of mixtures of tramadol hydrochloride and diclofenac sodium or of a salt of tramadol and diclofenac. The different spectrum indicates that a different chemical entity is present.

It is telling that although the Examiner argues that a compound would have different properties than the individual constituents from which it is formed, she then fails to address this Declaration evidence of different properties

which shows that the compound of the invention is something other than a simple mixture of tramadol hydrochloride and diclofenac sodium. She offers no explanation for these differences, but merely ignores them and treats the claim as if it said "mixture" instead of "compound." Applicants respectfully submit that this is error and warrants reversal of the rejection.

The Examiner's Complaint that the Composition Used The Declaration Tests Is Not the Same as the Claimed Composition is Misplaced

While it is true that the conventional pharmaceutical ingredients such as microcrystalline cellulose, lactose monohydrate and magnesium included in the test compositions of the Ziegler Declaration are not expressly mentioned in claim 17, this does not mean than the test compositions do not correspond to the claimed invention. The Examiner herself notes on page 6 of her Answer that the "comprising language" of the claim is "open." Thus the presence of these additional substances, which are needed for the formation of tablets for testing, does not take the test composition outside the scope of the claim. Rather the claim clearly reads on the test composition and the test composition is unquestionably a representation of the claimed invention. It would be highly impractical to attempt to form tablets for testing purposes without such conventional tableting ingredients. Importantly, however, the tablet compositions of the comparison mixture and of the compound of the invention are comparable, so that differences in properties can properly be attributed to

differences between a mixture of tramadol hydrochloride and diclofenac sodium and the compound of the invention.

Mauskop, US 5,914,129 does not describe a "Compound"
of Tramadol Hydrochloride and Diclofenac Sodium as Claimed

Mauskop discloses compositions containing one or more magnesium salts, one or more stimulants, and one or more analgesic agents (See claim 1). Mauskop further teaches that the one or more analgesic agents may include "at least two different non-opioid analgesic agents, at least two opioid analgesic agents, or at least one non-opioid analgesic agent and at least one opioid analgesic agent." (See column 3, lines 47-52). Mauskop includes long lists of opioid analgesic agents and non-opoid analgesic agents which include tramadol and diclofenac, respectively. Mauskop further states that his compositions may be in the form of capsules, cachets, tablets, powder, granules, a solution or suspension in an aqueous liquid or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion. (See column 6, lines 11-16.) Such a disclosure does not anticipate the presently claimed invention.

First, Mauskop does not actually disclose any composition containing both tramadol and diclofenac. It is only by first choosing the option of combining an opioid analgesic agent with a non-opioid analgesic agent and then making appropriate selections from the lists of opioid analgesic agents and non-opioid analgesic agents that one arrives at a composition containing both tramadol and diclofenac. Moreover, there is no guidance in Mauskop leading to the "right"

selections. This is not a proper basis for an anticipation rejection under 35 U.S.C. §102.

And second, even assuming *arguendo* that Mauskop did disclose a composition including tramadol and diclofenac, such a composition would only be a simple mixture, which the solubility curves and DSC spectra referred to above show is not the same as the claimed compound. As stated by the Examiner herself quoting MPEP §2112.01 at the bottom of page 6 of her Answer, "Products of identical chemical composition can not have mutually exclusive properties." It follows that the differing solubility and thermal decomposition properties shown for the claimed "Compound" in the Declaration evidence of record demonstrate that the claimed compound must necessarily differ in chemical composition from a mixture of tramadol and diclofenac as might result from someone serendipitously making appropriate selections from the lists of Mauskop.

Thus, Applicants respectfully submit that Mauskop does not anticipate their claimed compound of tramadol and diclofenac, and the rejection of claim 17 under 35 U.S.C. §102 over Mauskop should be reversed.

The Examiner's Arguments in Support of the
Obviousness Rejection of Claim 38 are also Flawed.

In attempting to defend the obviousness rejection of claim 38, which requires, among other differences, a repetition of steps which repetition is not disclosed or suggested in the record, the Examiner states that "the steps are repeated as necessary for the production of the desired tablet." This is exactly

the point. Repetition of the steps is not necessary for the production of the desired tablet of the reference. That is why the reference does not repeat the mixing and moistening steps as required by claim 38. The repetition is not necessary for production of the desired tablet and thus (absent an understanding of the principles of the present invention where the repetition of steps leads to formation of a compound of reduced solubility and consequent delayed release), the repetition a) would serve no known useful purpose, b) would only increase the complexity and expense of the production of the tablets, and c) would not be obvious.

Indeed, such repetition would be counterproductive to the object of Mauskop, who seeks rapid release and absorption. (see, e.g., column 2, lines 31-41). This is in distinct contrast to the present invention where the low solubility of Applicants claimed compound is useful to achieve a delayed and sustained release.

For these reasons, as well as the others discussed more fully in Applicants' original Brief on Appeal, Applicants submit that the method of claim 38 would not be obvious in view of Mauskop with or without *Remington's Pharmaceutical Sciences.*

SUMMARY AND CONCLUSION

The Examiner's rejections of claims 17 and 38 are based on a misconstruction of the claims. When the claims are properly construed, it is

apparent that the cited Mauskop reference neither discloses nor suggests the compound of the presently claimed invention nor the method by which it is made. Consequently the rejections under 35 U.S.C. §§ 102, 103 and 112 are erroneous and should be reversed.

Respectfully submitted,

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